Cardiomyocyte proliferation and progenitor cell recruitment underlie therapeutic regeneration after myocardial infarction in the adult mouse heart.

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Authors: Konstantinos Malliaras, Eduardo Marban

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Public Summary:
Myocardial infarction (heart attack) kills living heart muscle, leading to its replacement by scar tissue. Cell therapy utilizing injected cardiosphere-derived cells (CDCs) has been shown to be clinically effective in regenerating the heart by adding new living muscle and reducing the amount of scar tissue. However, the mechanism by which this occurs is unclear. This research demonstrated that, after myocardial infarction, the proliferation of resident heart muscle cells (cardiomyocytes) increases, but the majority of new cardiomyocytes arise from recruited endogenous stem cells. Cell therapy with CDCs cells boosts both adult cardiomyocyte proliferation as well as the recruitment of endogenous stem cells, resulting in the growth of new healthy heart muscle. Understanding the cellular sources of regenerating cardiomyocytes is the first step towards development of novel therapeutic strategies that can improve the efficacy of stem cell-based treatments and increase cardiomyoctye repopulation of infarcted myocardium.

Scientific Abstract:
Cardiosphere-derived cells (CDCs) have been shown to regenerate infarcted myocardium in patients after myocardial infarction (MI). However, whether the cells of the newly formed myocardium originate from the proliferation of adult cardiomyocytes or from the differentiation of endogenous stem cells remains unknown. Using genetic fate mapping to mark resident myocytes in combination with long-term BrdU pulsing, we investigated the origins of postnatal cardiomyogenesis in the normal, infarcted and cell-treated adult mammalian heart. In the normal mouse heart, cardiomyocyte turnover occurs predominantly through proliferation of resident cardiomyocytes at a rate of approximately 1.3-4%/year. After MI, new cardiomyocytes arise from both progenitors as well as pre-existing cardiomyocytes. Transplantation of CDCs upregulates host cardiomyocyte cycling and recruitment of endogenous progenitors, while boosting heart function and increasing viable myocardium. The observed phenomena cannot be explained by cardiomyocyte polyploidization, bi/multinucleation, cell fusion or DNA repair. Thus, CDCs induce myocardial regeneration by differentially upregulating two mechanisms of endogenous cell proliferation.